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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/419,305	10/15/1999	KAZUHIKO MARUTA	MARUTA=3C	1033

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EXAMINER	
PROUTY, REBECCA E	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 03/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/419,305	MARUTA ET AL.	
	Examiner	Art Unit	
	Rebecca E. Prouty	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 22 December 2003.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/22/03 has been entered.

Claim 1 is still at issue and are present for examination.

Applicants' arguments filed on 12/22/03, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim is indefinite in the recitation of "a variant of the enzyme obtainable by replacing..." as the

scope of the term "variant" is not clear. The claim is now limited to a variant of a variant of SEQ ID NO:1.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The recitation of "not having the amino acid sequences of SEQ ID NO:1, SEQ ID NO:3, and SEQ ID NO:4" introduces new matter into the claim. While the specification clearly discloses that the invention encompasses variants of SEQ ID NO:1 having one or more amino acid changes in the amino acid sequence of SEQ ID NO:1, there is no disclosure in the specification discussing making variants having changes specifically within SEQ ID NOS:3 and 4.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the enzyme of SEQ ID NO:1 or enzymes encoded by genes which will hybridize to SEQ ID NO:2 under specific

conditions, does not reasonably provide enablement for any enzyme with the claimed properties.

These claims are so broad as to encompass any enzyme with the claimed physicochemical properties which does not comprise the amino acid sequences of SEQ ID NO:3 or SEQ ID NO:4, including any naturally occurring enzymes with the claimed properties, and all functionally equivalent variants of such a naturally occurring enzyme. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of enzymes broadly encompassed by the claims. Neither the specification nor the prior art provide any guidance regarding additional sources of naturally occurring enzymes with the claimed properties. One of ordinary skill in the art would clearly be aware that enzymes with similar enzymatic activities can be highly diverse and often bear little or no homology to one another. This is particularly true where the enzymes are found within organisms which are evolutionarily highly diverse but is not uncommon even for two enzymes with the same organism or for enzymes encoded within evolutionarily similar organisms. As such one of ordinary skill in the

art would be unable to isolate such enzymes and their corresponding genes without undue experimentation to find a suitable source. Furthermore, the specification fails to provide enablement for all variants of the enzyme of SEQ ID NO: 1. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide sequence and the amino acid sequence of a single enzyme with the claimed properties.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a

reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass any enzyme with the claimed physicochemical properties because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting activity; (B) the general tolerance of such enzymes to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated

with the scope of the claims broadly including any enzyme with the claimed physicochemical properties. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of enzymes having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

The specification does not support the broad scope of the claims which encompass any enzyme with the claimed physicochemical properties because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting activity; (B) the general tolerance of such enzymes to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any enzyme with the claimed physicochemical properties. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of enzymes having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Applicants argue that the rejection under 35 U.S.C. §112, first paragraph is not proper because the specification teaches the properties of the claimed enzymes, methods for testing for enzymatic activity, thermostability, and methods for producing variants of a disclosed sequence are within the skill of the ordinary artisan. This is not persuasive because while methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan producing variants as claimed by applicants

(i.e., encoding a thermostable enzyme with a specific substrate specificity) requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute **undue** experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification. As previously stated the specification does not establish: (A) regions of the protein structure which may be modified without effecting activity and thermostability; (B) the general tolerance of such enzymes to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of

the essentially infinite possible choices is likely to be successful.

Furthermore while techniques such as discussed by applicants would be sufficient for one of ordinary skill in the art to make and use variants with only a few substitutions by making several variants and testing for those which retain the claimed properties, such experimentation would clearly be undue for those polypeptides with greater numbers of substitutions as the likelihood of a variant sequence retaining the claimed properties of the native polypeptide decreases substantially with each additional mutation while the number of possible variants which could be made increases exponentially. It is noted that variants with only a few substitutions are clearly within the scope that **has already been deemed enabled by the examiner**, however the claims do not in any way limit the number of alterations that can be present such that the scope of the claim encompasses enzymes with large numbers of alterations as well. As variants which retain the claimed physicochemical properties of the native polypeptide yet have large numbers of mutations are a very minute fraction of the possible

variants of the enzyme of SEQ ID NO:1 which could be made, the experimentation required to make and test all the possibilities would clearly be undue.

It should be noted that a conclusion of enablement or the lack thereof requires a consideration of several different factors including the breath of the claims (which in the instant case are enormously broad), the predictability of the art (which herein is highly unpredictable particularly for the enormous numbers of variants with major structural differences from the single disclosed species), the amount of guidance provided in the specification (which in the instant case amounts only to the provision of the structure of a single active species and assays to determine if any other protein is within the scope of the claim without any guidance as to which of the possible variants are likely to be successful) and the number of working examples (of which the instant specification provides none within the scope of the current claim as SEQ ID NO:1 is excluded therefrom). A review of all of these clearly leads to a conclusion that the enablement in the specification is **not** commensurate in scope with the current claim.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca Prouty, Ph.D. whose telephone number is (571) 272-0937. The examiner can normally be reached on Monday-Friday from 8:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Rebecca Prouty
Primary Examiner
Art Unit 1652